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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,170	07/20/2007	Gen-Sheng Feng	BURNHAM.010NP	7231
20995 7590 12/19/2011 KNOBBE MARTENS OLSON & BEAR LLP 2040 MAIN STREET FOURTEENTH FLOOR IRVINE, CA 92614			EXAMINER BERTOGLIO, VALARIE E	
			ART UNIT 1632	PAPER NUMBER
			NOTIFICATION DATE 12/19/2011	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/594,170	Applicant(s) FENG ET AL.	
	Examiner VALARIE BERTOGLIO	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10/24/2011.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 26,28-31 and 44-59 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 53-59 is/are allowed.
- 6) ☒ Claim(s) 26,28-31 and 44-52 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 September 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>10/24/2011</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's submission filed on 10/24/11 has been entered.

Claims 1-25,27,32-43 are cancelled.

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 28-31 and 44-52 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a genetically modified mouse whose genome comprises a Shp2^{flox} allele wherein the Shp2 gene is functionally disrupted in CamK2a-expressing cells such that no Shp2 is expressed in said cells and wherein said mouse exhibits increased body weight, early-onset obesity, and resistance to leptin, does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection is maintained for reasons set forth in the office action dated 08/19/2010 and reiterated in the office action dated 02/15/2011.

As previously set forth, the art has demonstrated other conditional knockouts of the Shp2 gene wherein loss of Shp2 expression from other cells types, resulting from use of different promoters driving Cre expression, leads to phenotypes other than those claimed and disclosed in the specification (for example, see Grossman, PNAS. 2009, 106:16704-16709; Nakamura, PNAS, 2009, 106:11270-11275). The art has also demonstrated that a non-conditional knockout of Shp2 in all cells of a mouse is embryonic lethal (Saxton, 1997, EMBO J, 16:2352-2364). Therefore, the specification enables making only a mouse lacking Shp2

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expression in CaMK2a-expressing cells with the claimed phenotypes. The phenotypes of other Shp2-disrupted mice would differ from those of the mice disclosed in the specification for the CaSKO mouse and therefore, the specification fails to enable those other mice encompassed by the claims. Use of other promoters would express in a different subset of cells of the forebrain and the effect of such an expression pattern is unpredictable for reasons previously made of record. As previously set forth, it would not be predictable that the claimed phenotypes would be obtained when using other forebrain-specific promoter that express in a different subset of forebrain cells as well as different cells outside the forebrain.

Applicant has amended the claims to limit the Shp2 gene disruption to at least a portion of neuronal forebrain cells with cells outside of the forebrain not comprising a Shp2 gene disruption. Applicant argues that promoters that drive expression in neurons are known and could be used to make the claimed mouse by driving Cre expression with those promoters, knocking out the Shp2 gene in Cre-expressing cells. This argument is not persuasive. The POMC and mNF-H promoters cited by Applicant differ in expression pattern from the CamK-2a promoter of the instant invention. These promoters are expressed outside the forebrain and would, therefore, knock out Shp2 gene expression outside the forebrain. As set forth previously, the CamK2a promoter drives expression only in the neurons of the hippocampus (a portion of the forebrain). Therefore, the specification only overcomes the unpredictability of phenotype of a genetic knockout when the Shp2 gene is knocked out only in hippocampal neurons. There is no evidence of record that any promoter other than the CamK2a promoter was known to have such an expression pattern and it was not known at the time of filing what phenotype would result from knocking out the Shp2 gene in neurons outside the hippocampal neurons.

It is also noted that the newly added limitation that cells outside the forebrain do not have a homozygous disruption of the endogenous Shp2 gene encompasses a mouse wherein

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there only needs to a single cell that does not comprise the genetic modification. The claim, when broadly interpreted, continues to read on use of any promoter as the claim requires "at least a portion of the forebrain" be genetically modified and that any number of cells, including just one cell, outside the forebrain not be modified. Due to efficiency of the technology of Cre-mediated recombination, a ubiquitous promoter could meet the limitations of the claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to VALARIE BERTOGLIO whose telephone number is (571)272-0725. The examiner can normally be reached on Mon-Fri 6:30-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio/
Primary Examiner, Art Unit 1632